**In the United States Patent and Trademark Office
on Appeal from the Examiner to the Board
of Patent Appeals and Interferences**

In re Application of:	George D. Purvis III
Serial No.:	10/655,870
Filing Date:	September 5, 2003
Examiner:	Mary K. Zeman
Group Art Unit:	1631
Confirmation No.:	7307
Title:	*Calculating a Potential of Mean Force (PMF) Score of a Protein-Ligand Complex*

Mail Stop: Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

Response to Notification of Noncompliant Appeal Brief

Appellant has appealed to the Board of Patent Appeals and Interferences from the decision of the Examiner sent electronically 16 April 2007, finally rejecting Claims 1-2, 5, 7, 9-12, 15, 17, 19-22, 25, 27, and 29-31, which are all pending in this case. Appellant filed 24 April 2007 a Notice of Appeal. Appellant filed 9 July 2007 an Appeal Brief. The Examiner mailed 9 August 2007 a Notification of Noncompliant Appeal Brief. In the Notification, the Examiner asserts that the Appeal Brief does not comply with 37 C.F.R. § 41.37(c)(1)(v). To expedite this Appeal, Appellant provides the attached Replacement Summary of Claimed Subject Matter. *See* M.P.E.P. ch. 1205.03 (Rev. 3, August 2005).

Conclusion

Appellant respectfully requests the Board of Patent Appeals and Interferences to reverse the Examiner's final rejection of the pending claims and instruct the Examiner to issue a notice of allowance of all pending claims.

The Commissioner is hereby authorized to charge any fee and credit any overpayment to Deposit Account No. 02-0384 of BAKER BOTTS L.L.P.

Respectfully submitted,
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Replacement Summary of Claimed Subject Matter

FIGURE 1 illustrates an example system 10 for calculating a PMF score of a protein-ligand complex. (Page 5, Lines 2-3). System 10 includes a computer system 12 and a PMF-scoring module 14. (Page 5, Lines 3-4). In particular embodiments, a module may include software, hardware, or both. (Page 5, Lines 4-5). Computer system 12 may enable a user to provide input to and receive output from PMF-scoring module 14. (Page 5, Lines 5-6). Computer system 12 may include one or more modules for generating one or more graphical user interfaces (GUIs) for providing input to and receiving output from PMF-scoring module 14. (Page 5, Lines 6-8). PMF-scoring module 14 may calculate one or more PMF scores of one or more protein-ligand complexes specified by a user and return the calculated PMF scores to the user. (Page 5, Lines 8-10). A PMF score of a protein-ligand complex may indicate the binding affinity between the protein and the ligand in the protein-ligand complex, and the binding affinity between the protein and the ligand in the protein-ligand complex may indicate the ability of the ligand to inhibit or otherwise modify the function of the protein. (Page 5, Lines 10-14). PMF-scoring module 14 includes a repulsion-term module 16 that may calculate one or more repulsion terms. (Page 5, Lines 14-16). PMF-scoring module 14 may use PMF-scoring data 18 to calculate a PMF score of a protein-ligand complex. (Page 5, Lines 16-17). PMF-scoring data 18 data that PMF-scoring module 14 may use to calculate a PMF score of a protein-ligand complex. (Page 5, Lines 17-19). In particular embodiments, PMF-scoring data 18 includes empirically derived parameters (such as minimum binding-energy distance and well-depth values) that may be used to calculated a PMF score of a protein-ligand complex. (Page 5, Lines 19-22).

To calculate a PMF score of a protein-ligand complex, PMF-scoring module 14 calculates a PMF score of each protein-ligand atom pair in the protein-ligand complex and combines the calculated PMFs with each other. (Page 5, Lines 29, through Page 6, Line 1). As an example and not by way of limitation, in particular embodiments:

$$\textit{PMF Score} = \sum_{r<r_{cutoff}}^{kl} A_{ij}(r)$$

$A_{ij}(r)$ is a PMF of a protein-ligand atom pair of atom-pair type ij at distance r, and kl is a protein-ligand atom pair of atom-pair type ij. (Page 6, Lines 1-5). A protein-ligand atom pair of atom-pair type ij includes a first atom of protein atom type i and a second atom of ligand atom type j. (Page 6, Lines 5-7). A PMF of a protein-ligand atom pair corresponds to

interaction energy between the two atoms in the protein-ligand atom pair. (Page 6, Lines 7-8). For purposes of calculating PMFs of protein-ligand atom pairs, protein atoms are defined by protein atom type and ligand atoms are defined by ligand atom type. (Page 6, Lines 8-10). Atom type is defined by element (carbon, oxygen, hydrogen, etc.) and local bonding environment (polar aliphatic, nonpolar aliphatic, polar aromatic, nonpolar aromatic, hydrogen bond donor, hydrogen bond acceptor, etc.). (Page 6, Lines 10-13). Examples of ligand atom types include nonpolar carbon sp^3 aliphatic; polar sp^3 carbon bonded to an atom other than carbon or hydrogen; sp nitrogen bound to one carbon; and other suitable ligand atom types. (Page 6, Lines 13-15). Examples of protein atom types include nonpolar aliphatic carbon; polar aliphatic sp^2 or sp^3 carbon bonded to atoms other than carbon or hydrogen; positively charged nitrogen; sulfur as hydrogen bond acceptor; nitrogen in a planar ring structure; and other suitable protein atom types. (Page 6, Lines 16-19). In particular embodiments, there may be thirty-four ligand atom types and sixteen protein atom types. (Page 6, Lines 19-20). Herein, reference to atom type includes protein atom type, ligand atom type, or both, where appropriate. (Page 6, Lines 20-21).

PMFs of protein-ligand atom pairs are derived from application of one or more atom-pair distribution functions to data that describes analyzed protein-ligand complexes, such as data from the BROOKHAVEN PROTEIN DATA BANK (PDB) or the PDB maintained by the RESEARCH COLLABORATORY FOR STRUCTURAL BIOINFORMATCIS (RCSB). (Page 6, Lines 22-26). As an example and not by way of limitation, in particular embodiments:

$$A_{ij} = -k_B T \ln\left[f^{j}_{vol\_corr}(r) \frac{\rho^{ij}_{seg}(r)}{\rho^{ij}_{bulk}} \right] = -k_B T \ln \rho^{ij}_{seg}(r) - k_B T \ln f^{j}_{vol\_corr}(r) + k_B T \ln \rho^{ij}_{bulk}$$

k_B is a Boltzmann factor, T is absolute temperature, $f^{j}_{vol\_corr}(r)$ is a ligand volume-correction factor, and ρ^{ij}_{bulk} is a number density of atom-pair type ij occurrences at a certain distance. (Page 6, Line 26, through Page 7, Line 5). In particular embodiments, to account for short-distance interaction between two atoms in a protein-ligand atom pair, a repulsion term is used to calculate a PMF of the protein-ligand atom pair. (Page 7, Lines 5-7). As an example and not by way of limitation, in particular embodiments, if two atoms in a protein-ligand atom pair of atom-pair type ij are separated from each other by a distance that is shorter than the

longest distance without an occurrence of atom-pair type *ij* in data that describes analyzed protein-ligand complexes, a repulsion term is incorporated into the above formula. (Page 7, Lines 7-11). In particular embodiments, if short-distance interaction between two atoms in a protein-ligand atom pair is greater than 4 kcal/mol, the above formula is replaced by a repulsion term. (Page 7, Lines 11-14).

A repulsion term corresponds to repulsive force between two atoms in a protein-ligand atom pair. (Page 7, Lines 15-16). Repulsive force causes two atoms in a protein-ligand atom pair to repel each other and may result from van der Waals (VDW) potential, electrostatic potential, and hydrogen bond potential between the two atoms. (Page 7, Lines 16-18). Although repulsive force is described as resulting from particular potentials, the present invention contemplates repulsive force resulting from any suitable combination of any suitable potentials. (Page 7, Lines 18-21). In particular embodiments, a repulsion term used to calculate a PMF of a protein-ligand atom pair is calculated according to (1) a minimum binding-energy distance of the protein-ligand atom pair and (2) a well depth of the protein-ligand atom pair. (Page 7, Lines 21-24). A minimum binding-energy distance of a protein-ligand atom pair is a distance between the two atoms in the protein-ligand atom pair that corresponds to a minimum binding energy between the two atoms in the protein-ligand atom pair. (Page 7, Lines 24-26). A well depth of a protein-ligand atom pair corresponds to an amount of binding interaction between the two atoms in the protein-ligand atom pair. (Page 7, Lines 27-28).

In traditional PMF scoring, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, a minimum binding-energy distance value is used that corresponds to a sum of VDW radii of the two atoms in the protein-ligand atom pair. (Page 8, Lines 1-4). In addition, in traditional PMF scoring, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, a well-depth value is used that corresponds to atom hardnesses of the two atoms in the protein-ligand atom pair. (Page 8, Lines 4-7). VDW radii account for VDW potentials, but do not account for other potentials (such as electrostatic potential and hydrogen bond potential) that may cause repulsive force, as described above. (Page 8, Lines 7-9). As a result, traditional PMF scoring does not account for potentials other than VDW potential that may cause repulsive force and, therefore, often generates inaccurate PMF scores of protein-ligand complexes. (Page 8, Lines 9-11).

In contrast, in particular embodiments of the present invention, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may use a minimum binding-energy distance value that corresponds to an empirically derived minimum binding-energy distance value. (Page 8, Lines 12-15). In particular embodiments, to calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may use a well-depth value that corresponds to an empirically derived well-depth value. (Page 8, Lines 15-18). In particular embodiments, each atom-pair type may correspond to an empirically derived minimum binding-energy distance value and an empirically derived well-depth value. (Page 8, Lines 18-20). To calculate a repulsion term that may be used to calculate a PMF of a protein-ligand atom pair, repulsion-term module 16 may determine an atom-pair type of the protein-ligand atom pair, access an empirically derived minimum binding-energy distance value and an empirically derived well-depth value that correspond to the determined atom-pair type, and use the accessed values to calculate the PMF of the protein-ligand atom pair. (Page 8, Lines 21-26).

FIGURE 3 illustrates an example method for calculating a PMF score of a protein-ligand complex. (Page 13, Lines 5-6). The method begins at step 100, where a user at computer system 12 specifies a protein-ligand complex for PMF scoring. (Page 13, Lines 6-7). At step 102, PMF-scoring module 14 accesses PMF-scoring data 18 associated with the specified protein-ligand complex. (Page 13, Lines 7-9). PMF-scoring data 18 may describe the protein and the ligand in the specified protein-ligand complex. (Page 13, Lines 9-10). As an example, PMF-scoring data 18 may describe the number of atoms and the type and position of each atom in the protein. (Page 13, Lines 10-11). As another example, PMF-scoring data 18 may describe the number of atoms and the type and position of each atom in the ligand. (Page 13, Lines 12-13). At step 104, PMF-scoring module 14 identifies a protein-ligand atom pair in the specified protein-ligand complex. (Page 13, Lines 13-14). At step 106, if a repulsion term should be used to calculate a PMF of the identified protein-ligand atom pair, the method proceeds to step 108. (Page 13, Lines 14-16).

At step 108, PMF-scoring module 14 accesses a table 30 of empirically derived minimum binding-energy distance and well-depth values. (Page 13, Lines 17-18). PMF-scoring data 18 may include table 30. (Page 13, Lines 18-19). At step 110, PMF-scoring module 14 uses table 30 to determine a minimum binding-energy distance value and a well-

depth value that correspond to the identified protein-ligand atom pair. (Page 13, Lines 19-21). At step 112, PMF-scoring module 14 uses the determined minimum binding-energy distance and well-depth values to calculate a repulsion term. (Page 13, Lines 21-23). At step 114, PMF-scoring module 14 uses the calculated repulsion term to calculate a PMF of the identified protein-ligand atom pair, at which point the method proceeds to step 118. (Page 13, Lines 23-25). At step 106, if a repulsion term should not be used to calculate a PMF of the identified protein-ligand atom pair, the method proceeds to step 116. (Page 13, Lines 25-27).

At step 116, PMF-scoring module 14 calculates a PMF of the identified protein-ligand atom pair without a repulsion term. (Page 13, Lines 28-29). At step 118, if a PMF of a protein-ligand atom pair in the specified protein-ligand complex has not been calculated, the method returns to step 104. (Page 13, Line 29, through Page 14, Line 1). At step 118, if a PMF of each protein-ligand atom pair in the specified protein-ligand complex has been calculated, the method proceeds to step 120. (Page 14, Lines 1-3). At step 120, PMF-scoring module 14 uses the calculated PMFs of the protein-ligand atom pairs in the specified protein-ligand complex to calculate a PMF score of the specified protein-ligand complex. (Page 14, Lines 3-5). At step 122, PMF-scoring module 14 communicates the calculated PMF score to the user at computer system 12, at which point the method ends. (Page 14, Lines 5-7).

Particular embodiments of the present invention may provide one or more technical advantages. (Page 3, Lines 14-15). Particular embodiments may be used to more accurately predict a structure of a protein-ligand complex. (Page 3, Lines 15-16). Particular embodiments may be used to more accurately calculate a binding affinity between a protein and a ligand and the positions of the atoms in the protein-ligand complex, which may help determine a mode of action of a ligand. (Page 3, Lines 16-19). Particular embodiments may be used to calculate a more accurate PMF score of a protein-ligand complex. (Page 3, Lines 19-20). In particular embodiments, a PMF score of a protein-ligand complex may be calculated according to more accurate PMF potentials that each account for multiple potentials (such as a van der Waals potential, an electrostatic potential, and a hydrogen bonding potential) that may cause repulsive force in a protein-ligand atom pair. (Page 3, Lines 20-24). Particular embodiments may be used to calculate a more accurate PMF potential between two atoms in a protein-ligand atom pair. (Page 3, Lines 24-25).

For the convenience of the Board, Appellants provide the following mappings of the claims here on appeal. Appellants do not necessarily identify all portions of the Specification and Drawings relevant to the recited elements of the claims. Appellants provide the following mapping not to limit the scope of the claims, but to help the Board make a decision on this Appeal.

Independent Claim 1 recites the following:

> An apparatus comprising:
> one or more processors; (e.g.: Figure 1; Page 5, Lines 2-28) and
> a memory coupled to the processors comprising one or more instructions, (e.g.: Figure 1; Page 5, Lines 2-28) the processors operable when executing the instructions to:
>
> determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex; (e.g.: Page 5, Line 29, through Page 6, Line 21)
>
> calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type; (e.g.: Page 6, Line 22, through Page 8, Line 26)
>
> calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; (e.g.: Page 6, Line 22, through Page 8, Line 26) and
>
> calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex. (e.g.: Page 5, Line 29, through Page 6, Line 21)

Independent Claim 11 recites the following:

> A method comprising:
> determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex; (e.g.: Page 5, Line 29, through Page 6, Line 21)
> calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type; (e.g.: Page 6, Line 22, through Page 8, Line 26)
> calculating a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; (e.g.: Page 6, Line 22, through Page 8, Line 26) and
> calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex. (e.g.: Page 5, Line 29, through Page 6, Line 21)

Independent Claim 21 recites the following:

Logic encoded in one or more media for execution and when executed operable to: (e.g.: Figure 1; Page 5, Lines 2-28)

determine an atom-pair type of a protein-ligand atom pair in a protein-ligand complex; (e.g.: Page 5, Line 29, through Page 6, Line 21)

calculate a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type; (e.g.: Page 6, Line 22, through Page 8, Line 26)

calculate a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; and

calculate a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex.

Independent Claim 31 recites the following:

A system comprising:

means for determining an atom-pair type of a protein-ligand atom pair in a protein-ligand complex; (e.g.: Figure 1; Page 5, Line 2, through Page 6, Line 21)

means for calculating a repulsion term of the protein-ligand atom pair according to a minimum binding-energy distance value and a well-depth value of the atom-pair type; (e.g.: Figure 1; Page 5, Lines 2-28; Page 6, Line 22, through Page 8, Line 26)

means for calculating a potential of mean force (PMF) of the protein-ligand atom pair according to the calculated repulsion term of the protein-ligand atom pair; (e.g.: Figure 1; Page 5, Lines 2-28; Page 6, Line 22, through Page 8, Line 26) and

means for calculating a PMF score of the protein-ligand complex according to the calculated PMF of the protein-ligand atom pair, the PMF score indicating a binding affinity between a protein and a ligand in the protein-ligand complex. (e.g.: Figure 1; Page 5, Line 2, through Page 6, Line 21)